-- VI --.

In Claim 30, line 3, change "III" to -- II --.

31. (Amended) A recombinant adeno-associated virus vector of claim 30 wherein said nucleic acid sequence [is responsible for encoding] encodes a human globin protein [or a biologically active fragment thereof], chosen from the human globin gene cluster.

REMARKS

Several minor errors which occurred throughout the specification have been corrected by the above amendments.

Applicants affirm the provisional election to prosecute the invention of Group I, Claims 1-35 and 39.

Declaration

The Office Action indicates that the Declaration is defective in that the third inventor has not given a post office address in the application papers as required by 37 C.F.R. 1.33(a). Applicant Arthur W. Nienhuis has provided his post office address under his signature, which is the same as his residence -- 647 West Drive, Memphis, TN; the zip code is 38112.

Rejections Under 35 U.S.C. § 112, first paragraph

The specification was objected to under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide an enabling disclosure. The Office Action states that certain recombinant adeno-associated virus vectors, rAAV/HS2/gamma globin/Neo, pJM24/vHS432γ, and pAAV/FACC/Neo "are required to practice the claimed invention." The Office Action continues that required elements must be known and readily available to the public or obtainable by a repeatable method set forth in the specification; this requirement can be satisfied by deposit of the vectors.

The objection is traversed on several points. Applicants disagree that the three particular vectors cited in paragraph 7 of the Office Action "are required to practice the claimed invention." These three vectors are specific embodiments of the claimed invention, but are clearly not the only vectors disclosed in and enabled by the specification. The invention is generally directed toward a recombinant

adeno-associated virus vector comprising at least a portion of the adeno-associated virus genome, at least one eukaryotic based *cis*-acting regulatory sequence, and at least one eukaryotic based nucleic acid sequence that encodes a therapeutic protein, wherein said virus vector has the property of regulating cell specific expression of said nucleic acid sequence(s) upon stable transduction of a target mammalian cell. This disclosure clearly encompasses more than the three vectors identified in the Office Action. For example, the vectors of the present invention can comprise HS-based promoter/enhancer fragments fused to globin genes or gene fragments. The specification also states that the present invention is not limited to rAAV vectors which comprise HS/globin constructs; any vectors which can be delivered to and expressed in a tissue specific manner within a mammalian host are contemplated. In addition, the specification indicates that the present invention is related to non-HS/globin constructs including, but not limited to, beta-galactosidase constructs. Listed as examples, but not limitations, in the specification are rAAV vectors directed towards use in liver specific expression of factor IX for treatment of hemophilia, expression of CTFR in the lung for treatment of cystic fibrosis, and expression of tyrosine hydrolase in brain tissue for treating Parkinson's disease. (See specification at page 7, lines 1-17 and page 8, lines 12-23.) Thus the invention can clearly be practiced with vectors other that those three listed in the Office Action.

Furthermore, the vectors claimed in the present invention are clearly enabled by the specification. For example, a recombinant AAV vector, pAAV/HSII$^{A}\gamma^{*}$/Neo, is illustrated in Figure 1 and discussed in Example 1. Construction of an rAAV plasmid containing FACC is described in Example 3 on page 35, line 31 through page 36, line 8. Construction of an rAAV-β-galactosidase vector is described on page 28, lines 3-12. Construction of plasmid JM24/vHS432$^{A}\gamma^{*}$ and preparation of rAAV is described on page 46, lines 8-20. Applicants respectfully submit that one skilled in the art could prepare any of the above vectors without undue experimentation based upon the teachings in the specification. Moreover, the techniques taught in the specification, in addition to the techniques for vector construction known in the art, could be employed to create all of the vectors covered by the claims of the present invention. Accordingly, Applicants respectfully submit that the specification is enabling as written, and no

deposit is required to meet the Section 112, first paragraph, requirements. Indeed, the Office Action even concedes that the specification teaches how to make an rAAV vector comprising a gamma globin, β-galactosidase, or FACC gene. (See Office Action at page 6, paragraph 9.)

For all of the above reasons, Applicants respectfully submit that the specification is enabling with respect to one skilled in the art.

Claims 18, 32, 35 and 38 were rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objections to the specification. For all of the reasons given above, Applicants respectfully submit that this claim rejection has been overcome.

Claims 1-35 and 39 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide enablement for a "biologically active fragment" of a protein. Applicants respectfully submit that the phrase "biologically active fragment" as used in the application would be understood by one skilled in the art to refer to a fragment of a protein that has the same biological activity as the full length protein. In an effort to advance this case to issuance, however, Applicants have deleted the phrase "biologically active fragment" from the claims in which it appears.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1, 12, 15, 17, 27 and 31 were rejected because the phrase "biologically active fragment" was deemed unclear; specifically, the Office Action states that "the size of the fragment is unknown, as is the type and range of biological activity" of the fragment. The phrase has been deleted from these claims, as well as from Claim 9, thereby obviating the rejection.

Claim 7 was rejected because the phrase "eukaryotic *cis*-acting regulatory sequence" lacked proper antecedent basis. Claim 7 depends from Claim 4, which depends from Claim 1; Claim 1 recites a eukaryotic based *cis*-acting regulatory sequence.

Claim 9 was rejected because the phrase "is responsible for encoding" is allegedly indefinite. Claim 9, as well as Claims 1, 12, 15, 17, 27 and 31, were amended to delete this language; the phrase "that encodes" or simply the word "encodes" was substituted therefor.

Claims 11, 14, 29 and 30 were rejected because the term "hypersensitive site IV" was repeated twice. Claims 11, 14 and 29, as well as Claim 8, were amended so that the second occurrence of "hypersensitive site IV" was replaced with -- hypersensitive site VI --. Support for this amendment is found throughout the specification, such as on page 4, line 6, page 6, line 20 and page 17, line 17. Claim 30, which was rejected on this basis, did not have two occurrences of the phrase "hypersensitive site IV" but rather two occurrences of the phrase "hypersensitive site III"; the second occurrence of this phrase was amended to read -- hypersensitive site II --. Support for this amendment is found, for example, on page 4, lines 5-10.

Effective Filing Date

The Office Action denies Claims 33-35 the benefit of the June 3, 1992 filing date. Claim 33 is directed to an rAAV vector comprising a DNA encoding a mild type Fanconi anemia C complementing protein; Claim 34 further defines the rAAV of Claim 33 as having a *cis*-acting regulatory element from the Rous sarcoma virus promoter region; and Claim 35 defines the vector of Claim 33 as pAAV/FACC/Neo^R. Applicants respectfully submit that this subject matter was disclosed in the application filed on June 3, 1992. Methods of using rAAV vectors with *cis*-acting regulatory elements are disclosed, as is the use of the rAAV to treat blood-related disorders. (See, for example, page 9, lines 15-20; and page 18, lines 15-16 and 19-23.) These passages were included in the specification as filed on June 3, 1992. Thus, the specific embodiments in Claims 33-35 are encompassed within the constructs disclosed in the original disclosure of the invention. Accordingly, Applicants respectfully submit that the claims are entitled to the June 3, 1992 filing date. Reconsideration of this point is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 1-26 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Walsh (Clin. Res. 39(2):325A, 1991). This rejection is respectfully traversed.

Applicants respectfully submit that the Walsh abstract is not an enabling teaching of the present invention. A reference cited under §102 must contain sufficient technical information to enable a person skilled in the art to make

and use the claimed invention without undue experimentation or unobvious contributions. (See, for example, In re: Hoeksema 399 F.2d 269, 158 USPQ 596, (CCPA 1968); In re LeGrice, 301 F.2d 929, 133 USPQ 365 (CCPA 1962). One skilled in the art simply could not, upon reading Walsh, construct a recombinant adeno-associated virus vector comprising at least a portion of the adeno-associated virus genome, at least one eukaryotic based *cis*-acting regulatory sequence, and at least one eukaryotic based nucleic acid sequence that encodes a therapeutic protein.

In addition, the abstract refers to only one embodiment of the present invention, and does not disclose the countless other embodiments encompassed by the claims. For example, the reference does not teach use of any therapeutic protein other than ^gamma globin, whereas the present invention is directed to a number of other eukaryotic based therapeutic proteins. Furthermore, the reference only discusses linking the DNA sequence encoding the protein to a site from the LCR, while the claim language encompasses linking the sequence to at least one of any eukaryotic based *cis*-acting regulatory sequences. Indeed, the specification indicates that the present invention also includes non-HS/globin constructs. Finally, the reference discloses utility only for sickle cell anemia and severe β-thalassemia. Again, the present invention is directed to the treatment of numerous other diseases as well.

In short, the Walsh reference discloses only one limited embodiment of the present invention and clearly fails to enable that embodiment; all of the other embodiments which Applicants contemplate and claim are similarly not enabled by the reference. Accordingly, Applicants respectfully submit that the reference is not an appropriate Section 102(b) reference and therefore does not defeat the patentability of Claims 1-26.

Claims 33-35 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Walsh et al. (Blood 82 (10 suppl. 1):347a, 1993). This rejection is respectfully traversed.

Claims 33-35 are generally directed to a recombinant adeno-associated virus vector comprising at least a portion of the adeno-associated virus genome, a eukaryotic based *cis*-acting regulatory sequence, and a eukaryotic based nucleic acid sequence that encodes a therapeutic protein. As discussed above, all of

the specific embodiments found in Claims 33-35 were adequately disclosed in the specification as originally filed. Accordingly, these claims are entitled to a filing date of June 3, 1992. The Walsh reference cited herein is dated December, 1993. Accordingly, the reference is not appropriately cited against these claims. Claims 33-35 are therefore allowable.

Rejections Under 35 U.S.C. § 103

Claims 27-32 and 39 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Walsh et al. (Clin. Res. 39(2):325A, 1991). This rejection is respectfully traversed.

Claims 27-32 and 39 are generally directed to a recombinant adeno-associated virus vector comprising at least a portion of the adeno-associated virus genome, a eukaryotic based *cis*-acting regulatory sequence, and a eukaryotic based nucleic acid sequence that encodes a therapeutic protein, wherein said virus vector has the property of regulatory cell specific expression of said nucleic acid sequence(s) upon stable transduction of a human hematopoietic cell. Claim 28 depends from Claim 27 and further defines said eukaryotic *cis*-acting regulatory sequence as being chosen from the region located from about hypersensitive site I to about hypersensitive site VI in association with the human globin gene cluster. Claim 29 depends from Claim 28 and further defines the eukaryotic *cis*-acting regulatory element as being chosen from the region located within the group of *cis*-acting regulatory elements consisting of HS I, HS II, HS III, HS IV and HS VI. Claim 30 depends from Claim 29 and further defines the *cis*-acting regulatory sequence as comprising HS IV, HS III and HS II. Claim 31 depends from Claim 30 and further defines the nucleic acid sequence as encoding a human globin protein chosen from the human globin gene cluster. Claim 32 depends from Claim 31 and further defines the virus vector as pJM 24/vHS432 $^{A}\gamma^{*}$. Claim 39 depends from Claim 37 and further defines the DNA sequence as encoding a wild type Factor IX protein.

The Office Action concedes that "Walsh does not teach the inclusion of all components of the locus control region, i.e. all of the hypersensitive sites, in a single vector, nor does he teach the inclusion of a gene for Factor IX protein in a recombinant adeno-associated viral vector. Furthermore, Walsh does not teach

transduction of human hematopoietic cells." Notwithstanding these significant shortcomings of the reference, the Office Action indicates that it would have been obvious to one skilled in the art to use hematopoietic cells instead of erythroid progenitor cells since both are immune cells. It would also have been obvious, according to the Office Action, to use the entire LCR region and to use Factor IX gene.

As discussed above, it is Applicants' contention that the Walsh abstract is not enabling for the present invention. It is limited to only one embodiment, and does not teach one how such an embodiment would be constructed. Accordingly, the reference cannot enable the numerous other embodiments of the present invention, encompassed, for example, in Claims 27-32 and 39. For this reason alone, Applicants submit that the rejection has been overcome.

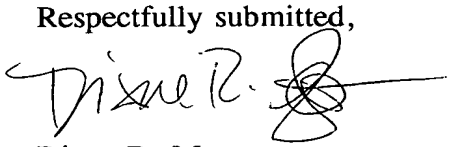
In any event, Applicants also submit that the reference does not teach or suggest the invention embodied in claims 27-32 and 39. The reference makes no suggestion that the entire LCR region be utilized. Nor does the reference suggest that the vector disclosed therein is useful for treatment of hemophilia B. Indeed, the reference specifically is limited to use in treating sickle cell anemia and β-thalassemia. Furthermore, the reference does not teach the use of hematopoietic cells. Even if erythroid cells and hematopoietic cells are both immune cells, there is no suggestion in the reference that the invention disclosed therein would be applicable to all immune cells or that one immune cell can be replaced with another. For all of theses reasons, Applicants respectfully submit that one skilled in the art would not have been motivated to create the invention presently claimed based upon the teachings of the reference, and that to do so would require a significant destruction of the teachings of the reference. The reference simply does not teach or suggest the invention embodied in Claim 27 and the claims which depend therefrom.

For all of the above reasons, Applicants respectfully submit that Claims 27-32 and 39 are patentable over the art.

SUMMARY

In summary, it is respectfully submitted that Applicants' Claims 1-35 and 39 are allowable as they are all patentably distinct from the art. Furthermore, Applicants respectfully submit that the specification, as well as the claims, clearly enable one skilled in the art to practice the invention. In addition, all of the rejections made under 35 U.S.C. § 112, second paragraph, have been overcome by the above amendments. Applicants therefore respectfully submit that the application is in proper form for issuance of a notice of allowance, and such action is respectfully requested at an early date.

Respectfully submitted,



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